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TITLE: Joint Distraction Treatments of Intra-Articular Fracture-Induced
Posttraumatic Osteoarthritis in a Large Animal Model

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14. ABSTRACT Post-traumatic osteoarthritis (PTOA) is a common complication after an intra-articular fracture (IAF) in both combat and civilian settings. The broad goal of this expansion award is to determine if joint distraction can prevent the development of PTOA after an IAF. During this second project year we continued analysis of the specimens generated during Project Year 1, developing and implementing new routines for confocal microscopy image analysis, contrast-enhanced micro CT analysis, and kinematic analysis. We also performed Western blots to analyze the synovial fluid harvested from the experimental joints. Results from this work corroborate our macroscopic finding that delays in fracture fixation do have a negative effect on cartilage, and immediate joint distraction did not have a therapeutic benefit. Our research team suffered a personal and professional loss with the death of our histologist which significantly delayed final histological analysis specimens from this first series. During this second project year we also completed all surgeries on the remaining animals in Specific Aim 1. Groups comparing immediate and delayed fracture fixation were completed in the spring and the remaining distracted group just prior to the end of the Project Year. Joint distraction was performed through the articulated distraction device that was developed this Year for use in the upcoming Aim 2 studies.					
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1. INTRODUCTION

Post-traumatic osteoarthritis (PTOA) is a severely debilitating degeneration of joints that frequently occurs after intra-articular fractures (IAFs) sustained both in military combat and training conditions and in active civilian populations. The purpose of this expansion project is to use the novel Yucatan minipig model of PTOA after IAF that was developed during our previous work (W81XWH-10-1-0864) to investigate the use of joint distraction to prevent development of PTOA subsequent to an IAF. Joint distraction has been found to be beneficial for treatment of late-stage osteoarthritis, when cartilage is all but absent in the joint. Our governing hypothesis is that distraction performed when cartilage is still present may have similarly positive effects for preventing joint degeneration. The effects of joint distraction applied acutely after IAF are the focus of Aim 1, and the effects of joint distraction applied shortly after the bone has healed are the focus of Aim 2. Of secondary interest are the effects of delayed fixation of a fracture (Aim 1), which is a common clinical practice in the treatment of IAF and almost universally a battlefield necessity. Also of secondary interest are the effects of articulated versus immobilized distraction (Aim 2) on both cartilage health and overall joint morbidity (arthrofibrosis, muscle weakness, etc.). Outcomes of both Aims investigating the effects of acutely applied and sub-acutely applied joint distraction will be a combination of macroscopic-level gait analysis for evaluating animal limb usage as a surrogate for function and pain, and microscopic/cellular levels of chondrocyte function and cartilage health. Upon conclusion of this project, we will have critically evaluated the use of joint distraction as a proactive treatment for PTOA.

2. KEYWORDS

Post-traumatic	Cartilage	Reactive Oxygen Species
Osteoarthritis	Gait Analysis	Mitochondrial Metabolism
Intra-articular Fracture	Joint Distraction	Western Blot
Yucatan Miniature Pig	External Fixator	Inflammation
Impact	Histology	Micro CT
Ankle	Mankin Score	

3. ACCOMPLISHMENTS

Due to challenges in obtaining animals of an appropriate age for our study, the timeline of the work performed in Project Year 2 has been significantly delayed from the timeline set forth in the Statement of Work (SOW). All accomplishments for Project Year 2 were related to Specific Aim 1, as Specific Aim 2 has yet to commence.

3.1 Major Goals

The goal of Specific Aim 1 was to determine if treating animals with an IAF of the hock with joint distraction at the time of fracture repair would preserve cartilage structure and function. There were two hypothesis associated with this aim. The first hypothesis was that a delay between fracture creation and fracture fixation (such as would be incurred in almost any human IAF scenario) would lead to more severe PTOA after 12 weeks in our minipig model. The second hypothesis was the joint distraction at the time of fracture fixation would preserve the health of the cartilage better than treating the fracture alone.

There were several activities that were to be completed in Project Year 1 that had not been finished at the time of the previous report. Primarily completion of Task 1.2, which was to complete our Aim 1 live animal work. Integrated within completion of that task was the design and construction of the articulated joint distractor (Task 3.1) which was also to have been completed during Project Year 1, but had not been at the time of the last report. Updates to the quantitative histological analysis programs (Task 2.3) were also not yet complete at the time of the previous report and continue to be ongoing.

There were also many tasks that were specifically planned to be completed during Project Year 2 in support of Aim 1. These tasks included analysis of contrast enhanced micro CT images and analysis of confocal images of the cartilage (Task 2.1), western blot analysis (Task 2.2), and histological and immunohistochemical analyses of cartilage (Task 2.4). Gait analysis was planned to be ongoing from Project Year 1 into Project Year 2 (Task 2.5).

3.2 Accomplishments

Specific Aim 1 Live Animal Surgeries – Tasks 1.2 and 3.1

The original planned live animal surgeries for Aim 1 included a total of 24 animals split evenly into three groups: immediate open reduction and internal fixation of the fracture (ORIF), a group with a three day delay between fracture and ORIF, and a group with a three day delay between fracture and ORIF that was then to receive acute joint distraction for a period of 6 weeks. Survival time is 12 weeks. A total of 12/24 animals were completed during Project Year 1. There were some moderate complications with the animals who wore the distractors (Figure 1). One animal jumped off the treadmill at 2 weeks, and broke their calcaneus pins. The distractor was removed at that time. The other three animals developed early pin loosening that was particularly pronounced in the calcaneus, and therefore the distractors were removed from this group at 4 weeks.

During final tissue harvest from this initial group of animals, we noted that the macroscopic images of the joints that had received joint distraction looked decidedly worse than the joints that did not undergo joint distraction (Figure 2). As distraction was intended to be therapeutic, and because of the pin loosening complications, we had serious concerns about using this approach in the remaining series of animals.

At the beginning of Project Year 2, we decided to proceed with analysis of the tissues harvested from the distracted group and let those findings guide our decision about how best to proceed with this group. To complete the other two groups of animals in Aim 1, the immediate ORIF and the three day delayed ORIF groups, we performed surgeries on eight minipigs in March (n=4 in each of these two groups). These animals completed their 12 week survival in June, and all tissues were harvested identically to the methods used for the first 12 animals. This resulted in completion of the

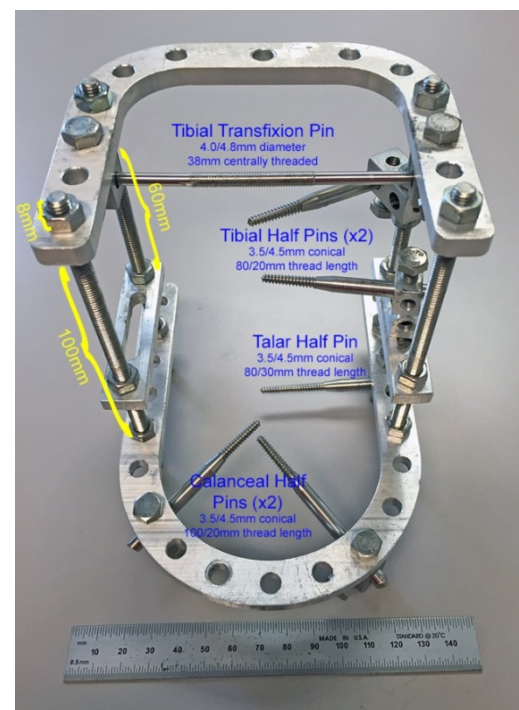


Figure 1. Minipig joint distractor developed and implemented in Project Year 1 animal surgeries.

originally planned n=8 immediate ORIF group, n=8 3-day delay in ORIF, and n=4 rigid distraction. Preliminary macroscopic findings indicate that the 3-day delay in ORIF has negative consequences on joint health, but analyses are not yet complete. With the exception of the final histological data from these animals, all data necessary data have been acquired at this stage to address Hypothesis 1a of Specific Aim 1.

As we proceeded with analysis of the data from the first 12 of the Aim 1 animals, it became clear that our rigid distraction approach was not beneficial to cartilage health (Figure 2). We discussed a modest change in approach with our Science Officer and decided to complete the remaining n=4 animals of Aim 1 using an articulated distractor. The reasons for this were two-fold. First, rigid distraction was not beneficial, and articulation has been shown to improve results of joint distraction. So it is possible that the motion allowed by the articulation would improve the therapeutic benefit of distraction.

Secondly, using the articulated design on these shorter term animals would allow us to determine complications associated with the articulated device prior to using that device on the Aim 2 pigs. In this way, the Aim 1 pigs were serving as a pilot experiment for the Aim 2 pigs, which are arguably higher risk because the groups for Aim 2 do not have distraction applied until 12 weeks after fracture and then go on for 6 months. A huge amount of resources will be invested in the Aim 2 animals before distraction is even applied, and it was therefore highly desirable to use the distraction device before use in this group.

We therefore emphasized the design and construction of the articulated distraction device, which was listed in the SOW as Task 3.1. We were very happy with the proximal portion of the distraction device, and no modifications were made to that portion of the design. After discussions among the traumatologist, veterinarians, and the PI, it was decided to undertake addition of two additional pins into the forefoot in addition to adding a hinge to provide articulation of the distractor. There were three design iterations of the hinge and forefoot pin hardware (Figure 3). As for the rigid versions of the distraction device, the different design iterations were trialed in several cadaveric pig hocks. The surgeries utilizing these devices were performed in the final month of Project Year 2 (Sept. 2017). This completes the live animal surgeries for Aim 1, and this final n=4 animals is presently completing their 12 week survival.

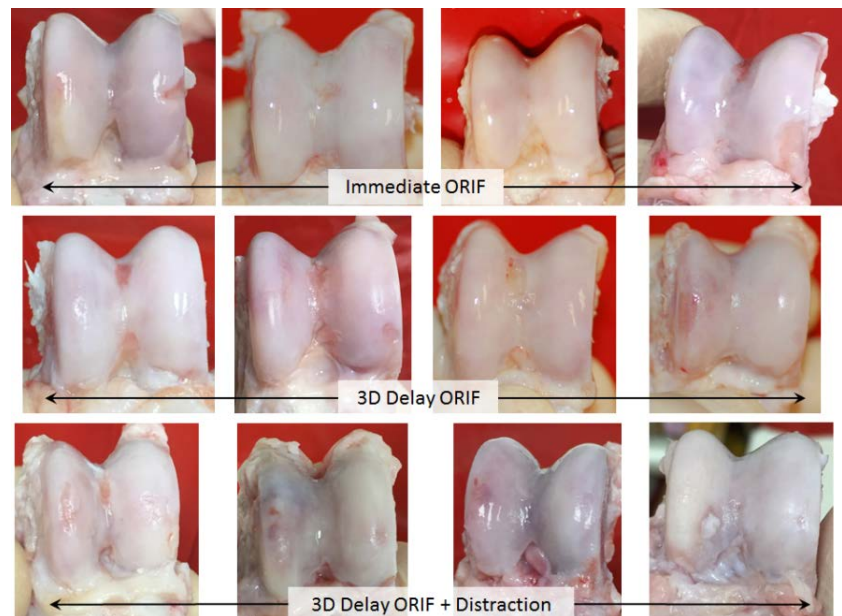


Figure 2. Composite of taluses from the first series of Aim 1 animals. Anterior is down and medial is on the left. A three-day delay appeared to be associated with thinner talar cartilage, and distraction appeared to result in larger erosions and discoloration of the underlying bone.

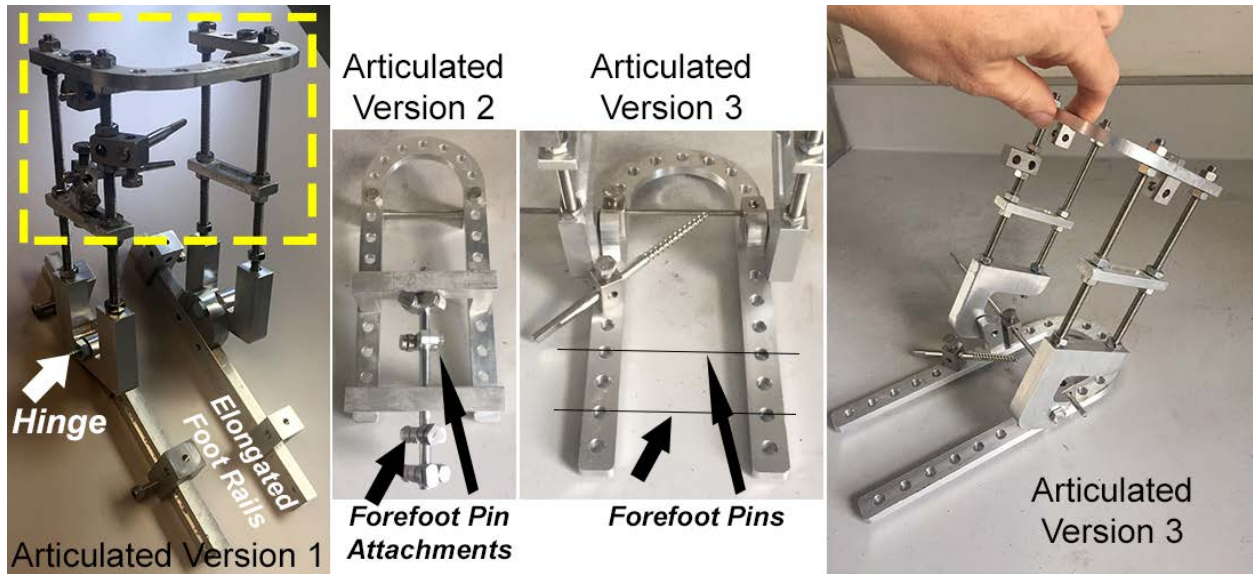


Figure 3. Design iterations of the articulated distraction device. The proximal portion of the rigid device was used as originally designed and implemented (dashed yellow box.). The originally proposed hinges were a U design to allow for a lateral radiograph of the talar dome. The initial elongated forefoot portion of the device was designed as rails, however concerns about the loss of stability from changing the distal part of the device into two unconnected sections causes a return to the original U shape ring for design iterations 2 and 3. The metatarsals of the minipig are arranged nonlinearly. To obtain best fixation of these bones, Version 2 was designed to interface with fixation pins inserted obliquely through all 4 tarsal bones. This design proved to be unnecessarily challenging to install. Thus the final version (Version 3) was designed to interface with two forefoot pins inserted through the two much larger central metatarsal bones and held with the same pin clamps as were used in Version 1. Moving to a calcaneal transfixion pin was discussed, but ultimately 2 or 3 half pins into the calcaneus were used.



Figure 4. Articulated distraction device as used in the final Aim 1 live minipig work. The proximal tibial design and fixation was identical to that used in the Project 1 series. The Y-shaped hinge and added forefoot pins were new design features of this device that permitted hock extension (left) and flexion (right) while maintaining joint distraction.

Micro CT and Confocal Image Analysis – Task 2.1

Contrast enhanced micro CT imaging was performed on all specimens that have been harvested to date. The scanning protocol involves soaking the formalin-fixed tissues in 60 mL of a solution consisting of 30% by volume Hexabrix and 70% PBS for 3 hours. Each specimen is then placed in the micro CT scanner sitting on top of piece of wet gauze to serve as a moisture source and prevent tissue dehydration. The cartilage is in air for the scan, which is performed at 9 micron resolution and takes 33 minutes for a tibial plafond and 67 minutes for a talar dome. Scans were all reconstructed with identical parameters to minimize beam hardening artifact and standardize image intensity within the bone (Figure 5).

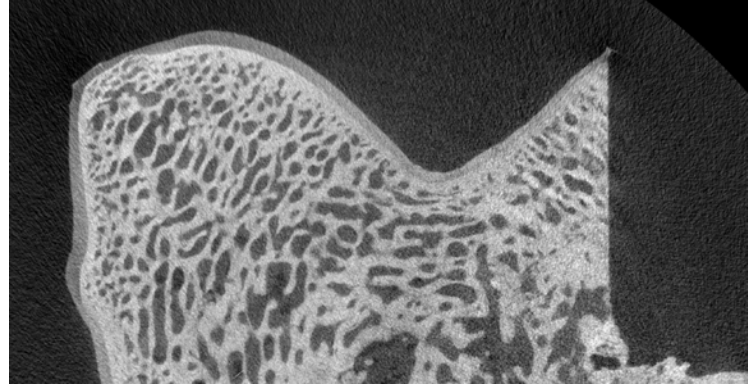


Figure 5. Micro CT image of a talus with contrast in the cartilage. The straight vertical line on the right is where the cuts were made to remove tissue for confocal microscopy and western blot analysis. The cartilage is bright indicating PG depletion, more focused on the remaining medial dome (right of image) and towards the valley on the lateral dome (left of image). Cartilage is readily visible for calculation of thickness maps over the surface.

For analysis, all images were reoriented to minimize the volume of interest and resampled in a sagittal plane. An automated routine was developed in Matlab to identify the cartilage/air interface.

Identifying the bone/cartilage interface was much more challenging, as cartilage with low proteoglycan content had much higher Hexabrix uptake, and we have thus far been unable to develop an automated routine that can reliably identify that boundary. Therefore we have been manually segmenting the bone cartilage interface. From these segmentations we can generate 3D maps of cartilage thickness to evaluate changes in cartilage thickness over the whole joint surface (Figure 6). Additionally we are developing routines to map proteoglycan content at different depths into the cartilage over the full joint surface (Figure 6). This will allow us to compare degenerative changes similar to what can be assessed using histological analysis over a much larger span of the joint. However, we still consider the compositional analysis preliminary as we have not yet had the opportunity to validate the Hexabrix technique for identifying proteoglycan content, which is a new technique to us, against the gold-standard histological sections from these specimens.

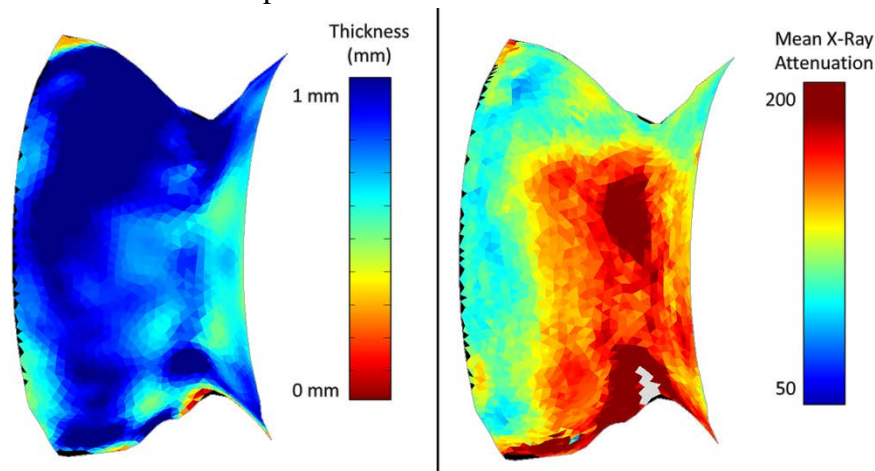


Figure 6. Maps of cartilage thickness (left) and superficial zone proteoglycan content (right) generated from micro CT analysis.

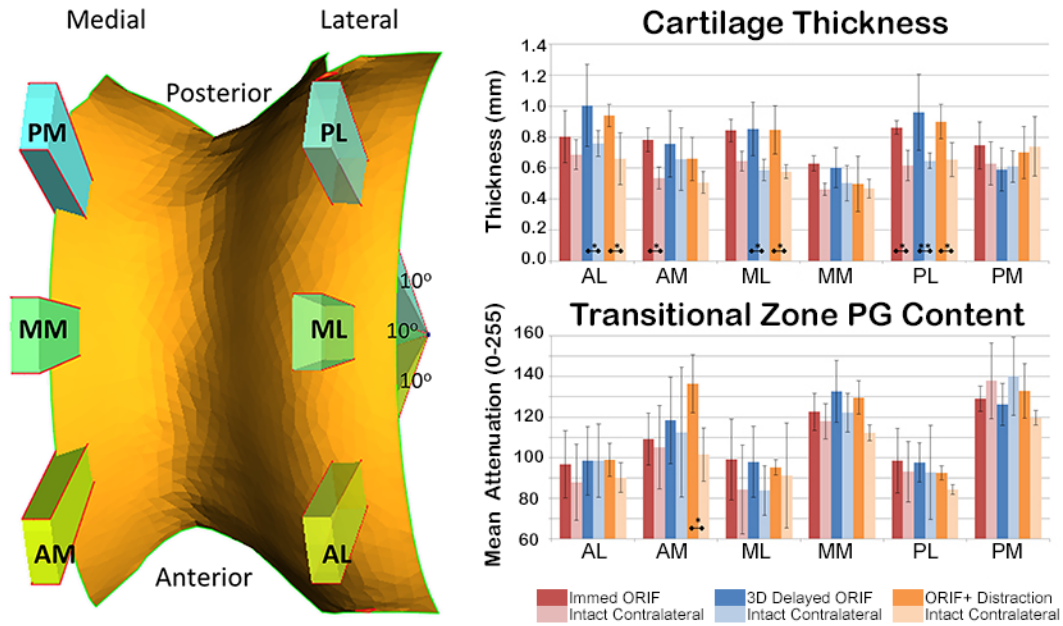


Figure 7. Preliminary sampling locations over the talar surface. Each region of interest was defined as a 10° arc of a best-fit cylinder to the talar dome and measured approximately 4 mm². Regions were defined as anterior, middle, and posterior on the medial and lateral sides. Cartilage thickness tended to increase relative to the non-operative contralateral joint, particularly on the lateral dome in the 3 day delay and distraction animals. There were localized increases in micro CT attenuation, indicating localized proteoglycan (PG) depletion in the fractured limbs, but limited statistical significance. These data are from the animals in Project Year 1, and thus there is n=4 per immediate, 3 day delay, and distraction groups. Once the remaining animals can be thus analyzed, the data can be finalized.

In the proposal we had planned to use a per-cell measure of oxygen consumption as a metric of chondrocyte oxidative stress and health. Early on in the project we elected to instead use a confocal imaging analysis approach to maintain spatial information about chondrocyte

mitochondrial function. We substituted using CellROX Orange and Mitotracker Deep Red during confocal imaging of viable cartilage to obtain the same information as was described in the proposal. In order to analyze the resulting images, our in-house confocal image analysis routine had to be adapted to our purpose. This involved modifying the routine to analyzed sagittally oriented sections image stacks (versus articular surface down), omitting analysis of visible bone, and accommodating different

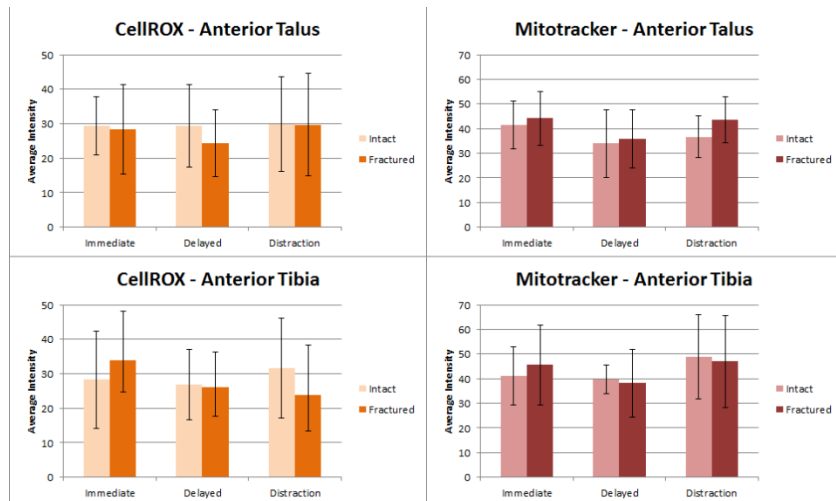


Figure 8. Average cellular intensity quantified from confocal microscopy images of viable cartilage at the time of harvest. The Immediate and Delayed groups are an average of n=8, Distraction is n=4. There is no loss of mitochondrial content, but subtle differences in oxidative measures depending on fracture treatment group.

staining intensities than Calcein AM and ethidium homodimer. Oxidative stress is indicated by an increase in CellROX, and the presence of functional mitochondria is indicated by Mitotracker. Preliminary analysis with our updated routine is indicating an average reduction in oxidative stress with injury, but a maintenance or even increase of mitochondrial content in the chondrocytes in the anterior part of the joint. Until the final histology for these specimens is available to assist with interpretation, these data are considered preliminary.

Western Blot Analysis – Task 2.2

Western blots have been used to analyze several key cartilage modifying proteins (MMP-3, MMP-13, TIMP-1, ADAMTS-5) from synovial fluid samples harvested from the first 12 Aim 1 animals at the time of euthanasia. These data will be used in conjunction with the immunohistochemical analyses that will be performed for the same factors. If it is decided upon analyzing the data from both methods that one is superior, the other may be omitted in subsequent study groups. The samples collected in Project Year 2 will be batch processed with the sample that will be collected from the ongoing remaining Aim 1 animals to ensure maximum consistency in technique.

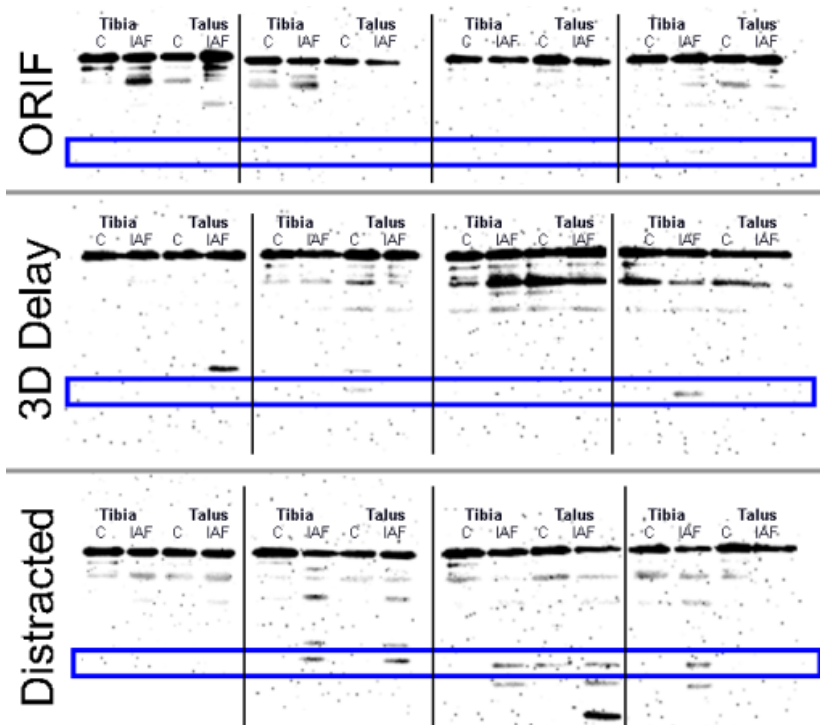


Figure 9. Western blots for TIMP-1. The location of the TIMP1 band is highlighted in blue. There are n=4 animals per group, separated by vertical black lines. TIMP-1 was most strongly expressed in the distracted group, indicating an effort at protection of the cartilage in this group.

Histological and Immunohistochemical Analysis – Task 2.4

Our research team suffered a great loss during Project Year 2 with the death of our histologist, Ms. Gail Kurriger. Ms. Kurriger suffered an accidental injury in April and passed away in July. Prior to those events, Ms. Kurriger had been performing histological processing on the specimens generated for Aim 1 in Project Year 1. While she was nearly ready to do the sectioning on those samples, she was not able to provide any histological sections during Project Year 2. Upon our loss, we identified an outside company to perform the histological processing of our specimens that were in progress at the time, as well as those that were generated from the animals utilized in Project Year 2. We identified, developed a protocol, contracted with, and shipped all of the Aim 1 specimens to Histon (<http://histon.com/histology.html>) for processing. The loss of Ms. Kurriger combined with the need to ship specimens to a company unfortunately delayed obtaining histological sections from the Aim 1 experiments during Project Year 2.

Gait Analysis – Task 2.5

In our previous report, we described the new animal gait lab available for use in this work. We also detailed the animal training protocol we developed to acclimate our study animals to walking on an instrumented treadmill for data capture. As described in the previous report, we train animals for 2 weeks prior to surgery and perform a preoperative data capture at healthy speed (1.8 km/hr) and a slow/postoperative speed (1.2 km/hr). Data captures were performed 1 week, 2 weeks, and 4 weeks postoperatively at the 1.2 km/hr speed. At the planned 6 week and 12 week capture times another 1.2 km/hr trial was captured, and if the animal was tolerant, a second 1.8 km/hr trial was captured.

We are in the process of analyzing the >200 data trials needed to establish the postoperative changes in kinematics for all of the animals in the different groups. At present, we have developed analysis code that will compute the flexion/extension, ab/adduction, and internal/external rotation of the pelvis relative to the room, the hip joint, the stifle/knee joint, the hock/ankle joint, and the metatarsal/toe joint. We have code that divides the multiple steps acquired during each data capture into individual step trials, which are then averaged to obtain a per animal average at each time point (Figure 10).

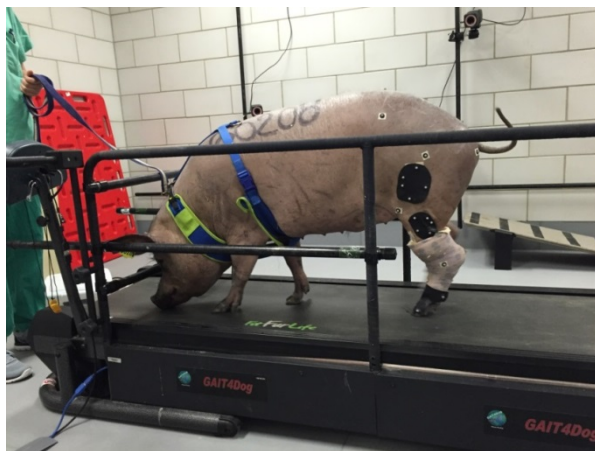
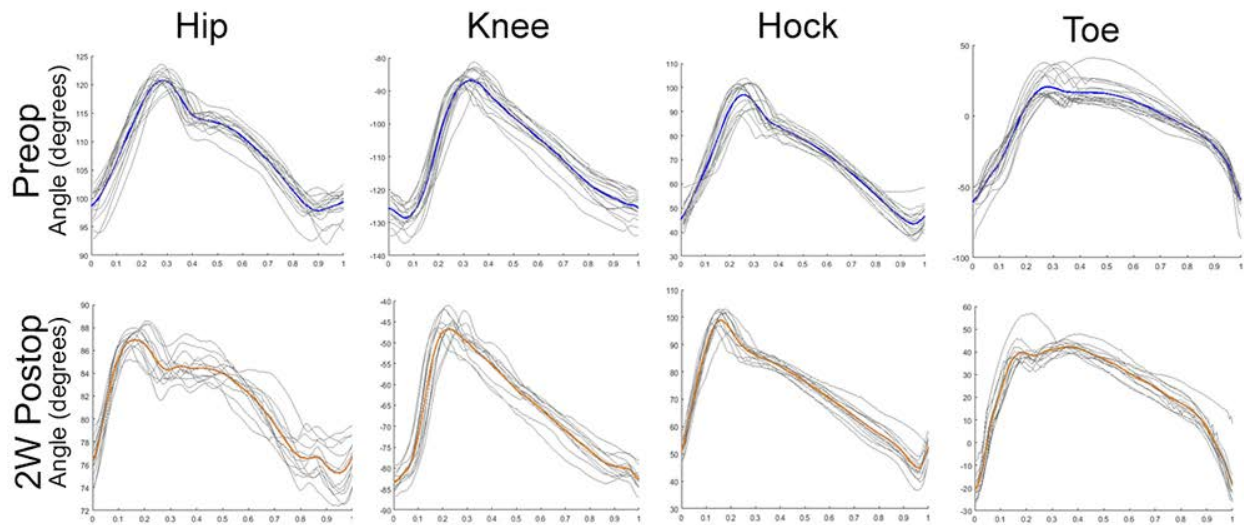


Figure 10. Yucatan minipig flexion extension angles measured preoperatively and 2 weeks postoperatively. Repetitive steps (toe-off to toe-off) from a single data capture are broken into individual steps (gray lines), normalized to step time, and then averaged for each animal at each time point (blue and orange lines). Joint motion can then be compared at postoperative time points. There is much greater variability in between steps in the postoperative time period compared to preoperative, most obvious for this comparison in the hip flexion/extension angles.

Our preliminary results evaluating changes in joint usage are very intuitive, with increased step time and decreased range of motion at the hock joint in the early postoperative period that returns or is trending towards the preoperative values. We are presently in the process of developing routines that will automatically discard abnormal steps from the per-animal average so as to not include any stumbles, jumps, or non-walking motions in the individual animal average. As these outliers cannot yet be automatically detected and excluded, which is important for our analysis of >200 trials, our solution is to not include any data from these animals in our working averages. This results in n values in the gait data lower than the n=8 of each group size. Additional animals' data must be added to these averages prior to drawing any final conclusions.

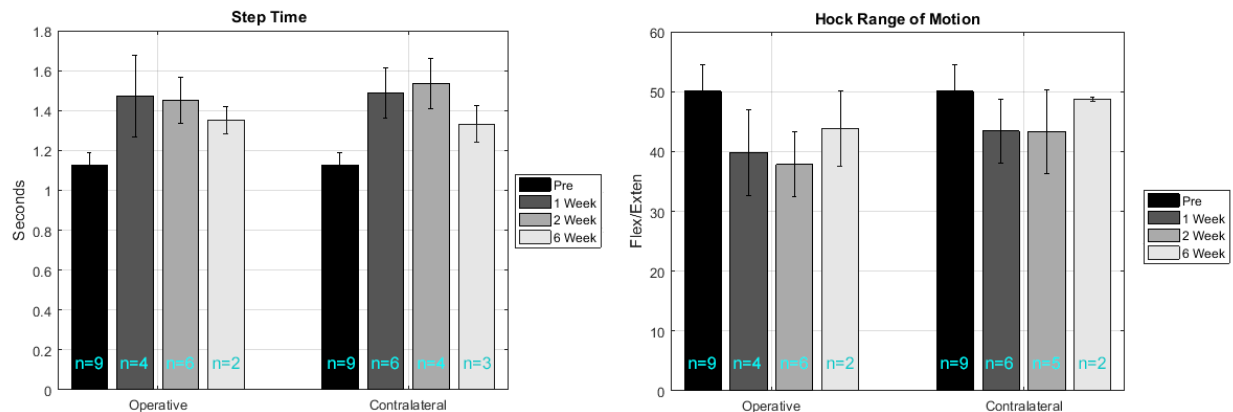


Figure 11. Effects of postoperative time on step duration and hock range of motion for animals that did not wear a joint distractor. 3day delay and immediate fixation groups have been pooled. The range of motion postoperatively on the operative side is not zero because the cast cannot completely immobilize the joint.

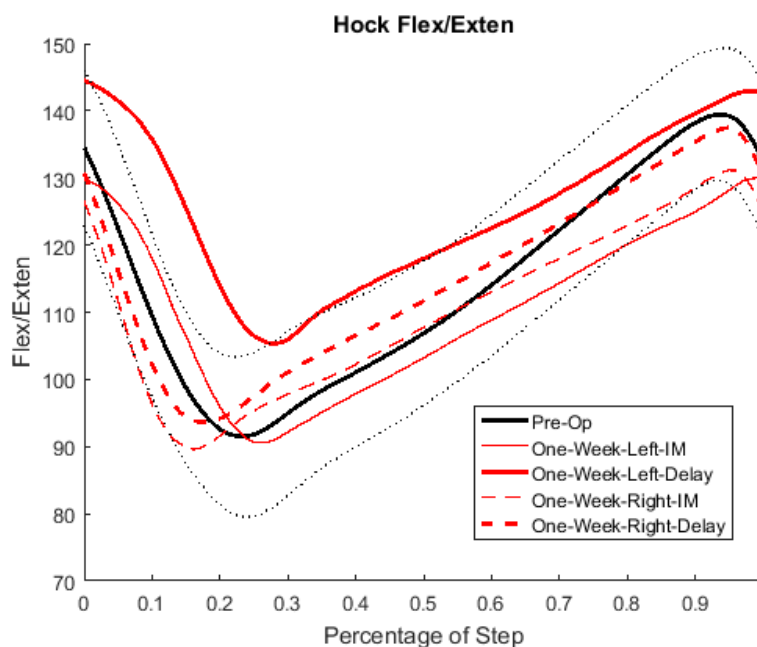


Figure 12. Hock flexion/extension angles preoperatively and 1 week postoperatively in the immediate (IM) and delayed fixation (Delay) groups. The intact contralateral (right) limbs had a similar motion pattern to the preoperative data. The fractured and treated hocks did not appear to have similar motion at 1 week, however n values included in this average are only half of the group size. It is therefore too early to conclude the effects of delayed fixation on postoperative limb kinematics.

3.3 Opportunities for Training & Professional Development

This project was not specifically intended to provide training or professional development. However, we do have a graduate research assistant working on the project who is receiving training in the form of one-on-one mentorship with the Project PI and several other research team members. The training has included learning the necessary skills for analyzing animal gait data and analyzing the mechanical effects of joint distraction. That training will contribute to the graduate student's thesis.

3.4 Dissemination of Results

We submitted two abstracts for consideration for presentation at the annual meeting of the Orthopaedic Research Society. At the time of this report, notices of acceptance had not yet been distributed.

1. Heck CR, Lauters AM, Watson NA, Fredericks DC, Goetz JE. Delayed fracture fixation does not cause additional limb dysfunction in a large animal model of post-traumatic osteoarthritis. 64th Annual Meeting of the Orthopaedic Research Society, March 10–13, 2018, New Orleans, Louisiana. (Submitted)
2. Heckelsmiller D, Femino EL, Watson NA, Heck CR, Fredericks DC, Goetz JE. Cartilage thickness and composition do not vary with time to fixation or distraction treatment in the short-term following intra-articular fracture of the distal tibia. 64th Annual Meeting of the Orthopaedic Research Society, March 10–13, 2018, New Orleans, Louisiana. (Submitted)

3.5 Plans for Next Reporting Period

Our plans for the next reporting period will focus on finalizing the data analysis for Aim 1 and beginning Aim 2. The final 4 animals receiving immediate distraction will end in the first quarter of Project Year 3. There will then be a waiting period into the second quarter of Project Year 3 to obtain histological sections back for those specimens. During that interim period we will perform histological analysis on sections for the immediate and delayed fixation group and focus our efforts on finalizing all data related to that hypothesis. A manuscript describing the effects of delayed fracture fixation will be written. This will require a substantial amount of cross-referencing between the contrast micro CT, confocal microscopy image analysis, Western blotting and immunohistochemistry data with the safranin-O stained histological sections that we considered the primary outcome measure of this work.

Upon receiving histological sections back from the remaining 4 animals that are presently in the joint distraction group, we will finalize the data from that hypothesis, contrasting or pooling the rigid and articulated data as appropriate. An additional manuscript describing these findings will be prepared, though likely not until the end of Project Year 3.

When we first became aware of the challenges in procuring animals of an appropriate age for our work, we identified a vendor willing to take a deposit in exchange for raising animals for our study. The first group of those animals will reach the necessary 2 year old mark in February, and the other group will reach the appropriate age in May. We will begin the surgical and live animal work of Aim 2 in the second quarter of Project Year 3. This will involve intensive periods of gait training, surgery and postoperative care, animal transfer and protocol updates.

Finally, as the final group of Aim 2 surgeries will not begin until May, and these are scheduled for a 6 month postoperative survival period, we will have to request a no-cost

extension to complete the live animal work and all followup analysis of Aim 2. That request will be submitted early in Project Year 3 to ensure sufficient time for the change to be made.

4. IMPACT

Given our delays in obtaining histological sections to support our preliminary findings from Aim 1, there is presently insufficient information available to yet have had an impact on clinical treatment of IAFs. We expect to soon be able to report on the effects of a delay in fracture fixation on cartilage health, though the impact of that report is yet somewhat unclear. This is because negative effects on cartilage health have to be balanced with immediate concerns of bony union and problems with adequate soft tissue coverage.

4.1 Impact on the Principal Discipline

The initial findings of this work would indicate that delays between an IAF and the time that fracture is surgically reconstructed increases cartilage degeneration that develops after IAF. Furthermore, distraction of a fractured joint, even for a small fraction of the total healing time also appeared to have negative effects on cartilage health. These findings were apparent macroscopically, but have also begun to be reflected in the microscopic and cell level analyses that have been ongoing throughout the project year. We expect these findings to be somewhat controversial as they would indicate that two extremely common practices related to fracture fixation, specifically a delay to allow soft tissues to recover prior to surgery and joint distraction to assist with bony healing, have negative effects on cartilage. It is not expected that this study will be enough evidence to immediately change clinical practice, but we expect these findings will initiate some discussion into optimal methods to treat IAFs without just considering the immediate injury.

4.2 Impact on Other Disciplines

Nothing to Report

4.3 Impact on Technology Transfer

Nothing to Report

4.4 Impact on Society

Nothing to Report

5. CHANGES/PROBLEMS

We have made a few changes to the specific tasks outlined in the original proposal as a result of several problems encountered over the first two years of work. These changes are a direct result of problems obtaining appropriately aged animals in addition to the negative results found while performing joint distraction in the first group of animals. All modifications are directly within the original goals of the proposed work and have been discussed with the Science Officer. They will be reflected in a modified SOW submitted at the time of the request for a no cost extension.

5.1 Changes in Approach

There were two primary changes in the approach to the work, neither of which change the underlying aims of the work. The first change was to modify the distraction being applied to

animals in Aim 1 to be an articulated distraction device, rather than the rigid distraction device described in the proposal and used for the first half of that experimental group. As mentioned above, this decision was made based on the uniformly negative effects of rigid distraction on the health of cartilage in the first 4 animals to which the device was applied. We could not in good conscience continue using this approach to treat the animals. The macroscopic evidence was the first of several pieces of data to support this, and all microscopic and cell-level data have supported this finding.

The second reason for changing to an articulated distractor to finish the Aim 1 animals was concerns about using the distraction device in the Aim 2 animals. While the Aim 1 animals are important, their total survival time is 12 weeks, and they wear the distractor only for the first part of that. If a complication were to arise necessitating early euthanasia, the total loss would be much less than the Aim 2 animals, which do not undergo distraction until 12 weeks after fracture, and which have a much longer survival period. Loss of one of these animals at the time of distraction would be much more detrimental to the study design and budget.

Therefore, we wanted to use the remaining Aim 1 animals to serve the dual purpose of studying the effects of joint distraction on cartilage health as well as simultaneously piloting the articulated distraction device prior to use on the Aim 2 animals. This allows us to complete our goal of investigating the effects of fixed versus articulated distraction, investigate the effects of immediate joint distraction on PTOA development after an IAF, and maximize changes of successful live animal experimentation in Aim 2.

The other major change in approach that was decided upon during Project Year 2 is the animal allocation for Aim 2. Originally, this Aim was designed to include a total of 40 animals, with $n=8$ distributed evenly among 5 study groups (controls, rigid distraction 18 wk, rigid distraction 26 wk, articulated distraction 18 wk, articulated distraction 26 wk). Unfortunately we only have 20 animals of an appropriate age available to complete this Aim. Given severe pin loosening that occurred when using the rigid distraction device, we elected to remove those groups from the planned Aim 2 experiments. In order to maintain our $n=8$ in the two different articulated distraction groups, we plan to reduce the group size in the control group to $n=4$. This was deemed acceptable because this control group is identical to other control animals we have done in the past. Many of the analyses methods we propose to use can be performed on remaining samples from those historic controls. The reason for not eliminating this group entirely is that not every analysis method can be performed on fixed tissue. This was a compromise to maintain power in our experimental groups and make use of existing historical controls.

These two changes in approach have been discussed with and approved with the Science Officer directing this project. They will be reflected in an updated SOW that will be submitted as part of a no-cost extension request that will be submitted early in Project Year 3.

5.2 Problems & Delays

The largest problem that occurred during Project Year 2 was the death of our histologist. This occurred before we obtained any histological sections from the animal experiments that had been completed in Project Year 1 and in the midst of the tissue harvest for the experiments that were performed in Project Year 2. Our histology needs are somewhat unique in that we require large osteochondral tissue sections that are very consistent in appearance for our image analysis routines to function. There is presently nobody on campus who was able to provide this service to us, which forced us to explore resources outside the University. We chose to work with a

private company, Histon, a company one of the members of our investigative team (Mr. Fredericks) has worked with previously. He highly recommended their work, and our Department agreed to make up any cost differential over what was in the budget for histological analysis as a result of sending our specimens out for processing. We hope to hire a replacement for Ms. Kurriger prior to the histological processing of the Aim 2 experiments.

This project remains significantly delayed as a result of the initial lack of appropriate animals. We have incurred no new delays beyond those incurred at the start of this work. Unfortunately, as these delays are mostly a result of waiting for animals to age, there is no way to accelerate the delayed work.

5.3 Changes in Expenditures

Current total expenditures at the end of Project Year 2, are \$832,154. This figure is lower than the original Project Year 2 budget. The reason for this is that we have not yet begun Aim 2 work, and we are waiting to post charges for the final Aim 1 animals until those animals have finished their full survival time. Those charges will post in December 2017, when the animals complete their survival time. Provided there are no unexpected complications, these charges will be approximately \$18,000.

While the overall expenditures are less than the original project timeline, this project is actually running over budget. That is because we have had to purchase animals from a much more expensive vendor and move per diems into later years of the project when costs have escalated. This year we have also incurred additional expense of needing to send our histology to a private company to ensure the timeliest completion. We expect to be able to balance costs by using a reduced number of animals in Aim 2 and housing these animals at Iowa State University, which has less expensive per diem rates. As part of a no cost extension we will perform a full re-budgeting of all remaining project activities. We will modify efforts and analysis methods as needed to meet the aims of the project within the remaining funds.

5.4 Changes in Use/Care of Human Subjects

Not Applicable

5.5 Changes in Use/Care of Vertebrate Animals

There were a total of 6 amendments to the approved animal care protocol during Project Year 2. Four of those amendments were addition of technical personnel based in the Animal Surgicenter who assist with within building transportation of the animals for weighing, preoperative surgery, etc. One amendment was for an additional sedation drug to improve animal comfort, and the final amendment was to permit acquisition of an as-needed postoperative CT scan to check for complications with fracture healing or surgical fixation. IACUC and ACURO approval will be obtained prior to a change in housing location for the Aim 2 animals that will be used in the upcoming Project Year 3 activities.

5.6 Changes in Use of Biohazards/Select Agents

Not Applicable

6. PRODUCTS

As described in section 3.4, we submitted two abstracts for consideration. Acceptance notices are anticipated in November 2017. No publications or presentations have yet occurred.

1. Heck CR, Lauters AM, Watson NA, Fredericks DC, Goetz JE. Delayed fracture fixation does not cause additional limb dysfunction in a large animal model of post-traumatic osteoarthritis. 64th Annual Meeting of the Orthopaedic Research Society, March 10–13, 2018, New Orleans, Louisiana. (Submitted)
2. Heckelsmiller D, Femino EL, Watson NA, Heck CR, Fredericks DC, Goetz JE. Cartilage thickness and composition do not vary with time to fixation or distraction treatment in the short-term following intra-articular fracture of the distal tibia. 64th Annual Meeting of the Orthopaedic Research Society, March 10–13, 2018, New Orleans, Louisiana. (Submitted)

This work was selected to be a research highlight for the Peer Reviewed Orthopedic Research Program on the CDMRP website:

- http://cdmrp.army.mil/prorp/research_highlights/17goetz_highlight.aspx

The primary product developed in this reporting period was the articulated external fixator for applying distraction to the minipig hock. There are no intentions to pursue a patent for this device as it is simply specific hardware to this project and has very limited other applications.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1 Individuals Working on the Project

Jessica Goetz	Project PI
Nearest person month Worked:	3
Contribution to Project:	Dr. Goetz has been actively involved in designing and testing the external fixator, assisting with the gait analysis, live animal surgery, and followup gait analysis and care. She performed the micro CT scanning and guided the analysis. She has also been performing administrative and organizational duties, writing reports, managing budgets and coordinating the research team.
Funding Support:	Dr. Goetz was supported by funds from the NIH, the Arthritis Foundation, Mortise Medical LLC, and the University of Iowa Department of Orthopedics and Rehabilitation in addition to this award.
Thomas Baer	Engineer
Nearest Person Month Worked:	2
Contribution to Project:	Mr. Baer was responsible for layout and building of the multiple iterations of the articulated distraction devices described in this report. This includes the incremental version modifications and large scale production to build multiple full versions for the live animal work.
Funding Support:	Mr. Baer was supported by funds from the NIH and the University of Iowa Department of Orthopedics and Rehabilitation in addition to this award.

Mitchell Coleman

Nearest Person Month Worked:

Contribution to Project:

Co-Investigator

1

Dr. Coleman was responsible for guiding the biological and histological analysis techniques initiated during euthanasia. He identified the new mitochondrial confocal microscopy stains and developed the protocols for their implementation. He assisted with Western blot analysis and supervised changes to the confocal imaging analysis routine.

Funding Support:

Dr. Coleman was supported by funds from the NIH and the University of Iowa Department of Orthopedics and Rehabilitation in addition to this award.

Douglas Fredericks

Nearest Person Month Worked:

Contribution to Project:

Co-Investigator

1

Mr. Fredericks assisted with modifications to animal care documents, assisted with the performance of the all surgeries, and assisted with general project planning.

Funding Support:

Mr. Fredericks was supported by funds from Bioventus LLC, Baxter Healthcare Corp., Medtronic Sofamor Danek, Inc., Implanet America Inc., SIRA KOSS, Berkeley Advanced Biomaterials, OrthoRebirth Ltd., the NIH, the Arthritis Foundation, W81XWH-14-1-0163, and W81XWH-14-1-0327, in addition to this award.

Christopher Heck

Nearest Person Month Worked:

Contribution to Project:

Graduate Research Assistant

6

Mr. Heck has been learning/implementing quadruped gait analysis techniques and assisted with all surgeries and follow up care, dissection, and confocal imaging.

Funding Support:

Mr. Heck was supported entirely by this award.

Emily Petersen

Nearest Person Month Worked:

Contribution to Project:

Veterinarian

1

Dr. Petersen organized all animal ordering, animal surgeries and performed all postoperative care. She assisted in modifications to animal care documents and with gait analysis.

Funding Support:

Dr. Petersen was supported by funds from Bioventus LLC, Baxter Healthcare Corp., Medtronic Sofamor Danek, Inc., Implanet America Inc., SIRA KOSS, Berkeley Advanced Biomaterials, OrthoRebirth Ltd., the NIH, the Arthritis Foundation, W81XWH-14-1-0163, and W81XWH-14-1-0327, in addition to this award.

Michael Willey

Nearest Person Month Worked:

Contribution to Project:

Co-Investigator

1

Dr. Willey provided clinical expertise used to design the different fixator hardware systems, and performed all the live animal surgeries.

Funding Support:

Dr. Willey was supported by funds from his clinical appointment at the University of Iowa Department of Orthopedics and Rehabilitation and the VA hospital in addition to this award.

Other Personnel

Many additional personnel contributed to this project. Several were paid through this grant, though with efforts less than 1 person month thus they are therefore not listed above. These individuals were supported the companies listed for key personnel, other grants from the National Institutes of Health and the Department of Defense. The remainder was supported by the University of Iowa Department of Orthopedics & Rehabilitation.

James Martin – biological analysis input

Gail Kurriger – dissection, histology

Barb Laughlin – dissection

Abigail Lehman – dissection

Marc Brouillette – confocal microscopy

Cheng Zhou – Western blotting

M. James Rudert – mechanical testing

Nicole Szabo – confocal image analysis

Keli McLaughlin – animal monitoring

Amie Pluskowski – gait analysis

Amanda Weibold – animal monitoring

Nicole Watson – gait analysis

7.2 Changes in Active Other Support

The last update in Other Support for key investigators was made in the previous annual report. All updates in completed support and new support reported here are relative to that time.

Goetz – Dr. Goetz concluded her involvement with two previous projects, extended two ongoing projects and began two new grants since the previous reporting period.

Completed:

1. Non-Surgical Treatment of Arthrofibrosis CDMRP W81XWH-14-1-0327

Sponsor Agency: US Department of Defense,

09/01/2014–08/31/2018, \$1,098,613

James A. Martin, PhD (PI)

Jessica E. Goetz, PhD (Co-Investigator), 1.2 Calendar months

2. Finite Element Analysis of RSA

Sponsor Agency: Tornier, Inc.

07/15/2015 – 07/15/2018, \$58,478 Total Costs

Carolyn M. Hettrich, MD, MPH (PI)

Jessica E. Goetz, PhD (Co-Investigator), 0.6 Calendar months

Extended:

1. Dynamic Ultrasound Measurement of Median Nerve Kinematics in the Carpal Tunnel

5 R03 AR062729-03

Sponsor Agency: US DHHS, National Institutes of Health/NIAMS

09/01/2012–08/31/2018, No Cost Extension, Award \$226,500

Jessica E. Goetz, PhD (PI), 1.2 Calendar months

2. CORT Innovations to Assess and Forestall Post-Traumatic Osteoarthritis

5 P50 AR055533-05

Sponsor Agency: US DHHS, National Institutes of Health/NIAMS

09/01/2012–08/31/2018, No Cost Extension, Award \$7,038,002

Joseph A. Buckwalter IV, MD, MS (PI)

Jessica E. Goetz, PhD (PI-Biomechanics and Imaging Core), 1.8 Calendar months

New:

1. Joint Contact Stress as a Tool for Clinical Decision Making in Periacetabular Osteotomy

Sponsor Agency: Orthopaedic Research and Education Foundation

9400 West Higgins Road, Suite 215

Rosemont, IL 60018-4975

07/01/2017–06/30/2020, \$209,804 Total Direct Costs

Jessica E. Goetz, PhD (Co-PI), 1.2 Calendar months

Project Goals: This is a project to use computational stress analysis (discrete element analysis, or DEA) to advance our understanding of how acetabular reorientation affects the contact mechanics of the dysplastic hip joint and how that influences patient outcomes.

Specific Aims: Specific Aim 1 is to measure changes in contact stress in patients treated with PAO for treatment of hip dysplasia and correlate those changes with patient-reported clinical outcomes at greater than 5 year follow up. Specific Aim 2 is to develop a technique of “virtual PAO” to pre-operatively template optimum position of the acetabulum and assess a surgeon’s ability to achieve this position during surgery. Specific Aim 3 is to develop a technique to interface DEA with standard intra-operative fluoroscopic images to provide surgeons with real time assessments of contact stress and proximity to optimum PAO position.

OVERLAP: There is no overlap with this work.

2. Mortise Medical Research Study

Sponsor Agency: Mortise Medical, LLC

124 South 600 West, Suite 100

Logan, Utah 84321

01/01/2017–12/31/2017, \$100,620 Total Direct Costs

Jessica E. Goetz, PhD (PI), 2.4 Calendar months

Project Goals: This project will consist of determining if a mechanically controlled surgical technique, a more anatomic reconstruction method, or a combination of those interventions will result in better anatomic function of an injured distal tibiofibular syndesmosis.

Specific Aims: Aim 1 of this project is to investigate the effects of well-controlled forces and positions of surgical reduction clamping will be investigated using an instrumented force clamp during a cadaveric CT reduction study. Aim 2 of this

work is to perform a direct biomechanical measurement of ankle kinematics during a rotational stress test under a variety of existing and new syndesmotomic repair techniques.

OVERLAP: There is no overlap with this work.

Coleman – Dr. Coleman had one large grant close, an extension of an ongoing grant and received a K99/R00 grant from the NIH since the last report.

Completed:

1. Mitochondrial Based Treatments that Prevent Posttraumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model
W81XWH-11-1-0583
Sponsor Agency: United States Department of Defense, Army Medical Research Acquisition Activity
09/01/11 – 08/31/2017, \$2,559,912 Total Costs
James A. Martin, PhD (PI)
Mitchell C. Coleman, PhD (Co-Investigator), 3.00 Calendar months

Extended:

1. CORT Innovations to Assess and Forestall Post-Traumatic Osteoarthritis
5 P50 AR055533-05
Sponsor Agency: US DHHS, National Institutes of Health/NIAMS
09/01/2012–08/31/2018, No Cost Extension, Award \$7,038,002
Joseph A. Buckwalter IV, MD, MS (PI)
Mitchell C. Coleman, PhD (Co-Investigator), 1.8 Calendar months

New

1. Do Changes in Thiol Metabolism Mediate Osteoarthritis Progression?
1 K99 AR070914-01A1
Sponsor Agency: US DHHS, National Institutes of Health/NIAMS
One Democracy Plaza, 6701 Democracy Blvd, Suite 800
Bethesda, Maryland 20892-4872
09/01/2017–08/31/2021, \$90,961 total costs K99
Mitchell C. Coleman, PhD (PI), 9.0 Calendar months
This career development project is focused on orthopedic training and conducting novel research into the roles of Nrf2 and Bach-1 during chronic oxidative stress and after mechanical injury in hopes of establishing a new, independent line of research. This will be done under the guidance of primary mentor, Dr. James Martin, an expert in orthopaedic cell biology with over 30 years' experience in research and training; co-mentor for redox biology, Dr. Douglas Spitz, an expert in redox biology with 30 years of continuous independent NIH funding and training experience including an NIH T32 and several K-award mentorships; and clinical co-mentor, Dr. Larry Marsh, a world class trauma surgeon and clinical researcher with experience in training clinical and basic scientists. These mentors will guide the acquisition of preliminary data for design of an adeno-associated

virus to disrupt thiol metabolism and redox signaling, job search and negotiation process for a tenure track position, execution of the R00 research into the role of thiol metabolism after injury, and composition of an R01.
OVERLAP: There is no overlap.

Fredericks – Mr. Fredericks has completed involvement in 6 previous grants/contracts and started 6 new since the previous report.

Completed:

1. ReBOSSIS in a Lapine Posterolateral Fusion Model and ReBOSSIS Bone Void Filler in a Rabbit Metaphyseal Defect Model
Sponsor Agency: OrthoRebirth Co, Ltd.
04/25/2016–08/31/2017, \$438,351 Total Direct Costs
Douglas C. Fredericks (PI), 0.12 Calendar months
2. Engineering Endogenous Cartilage Repair
Sponsor Agency: Arthritis Foundation
01/01/2016–01/01/2019, \$892,057 Total Direct Costs
James A. Martin, PhD (PI)
Douglas C. Fredericks (Co-Investigator), 0.6 Calendar months
3. Silhouette Lapine Posterolateral Fusion Model
Sponsor Agency: Biostructures, LLC
09/01/2015–12/01/2016, \$235,019 Total Direct Costs
Douglas C. Fredericks (PI), 1.2 Calendar months
4. Intra-articular Lubricin Gene Therapy for Post-traumatic Arthritis
W81XWH-14-1-0163
Sponsor Agency: US Department of Defense, Congressionally Directed Medical Research Program
08/15/2014–08/14/2017, \$493,234 Total Direct Costs
James A. Martin, PhD (PI)
Douglas C. Fredericks (Investigator), 1.2 Calendar months
5. CORT Innovations to Assess and Forestall Post-Traumatic Osteoarthritis
5 P50 AR055533-05
Sponsor Agency: US DHHS, National Institutes of Health/NIAMS
09/01/2012–08/31/2018, No Cost Extension, Award \$7,038,002
Joseph A. Buckwalter IV, MD, MS (PI)
Douglas C. Fredericks (Investigator), 2.9 Calendar months
6. Mitochondrial Based Treatments that Prevent Posttraumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model
W81XWH-11-1-0583
Sponsor Agency: United States Department of Defense, Army Medical Research Acquisition Activity
09/01/11 – 08/31/2017, \$2,559,912 Total Costs
James A. Martin, PhD (PI)
Douglas C. Fredericks (Investigator), 1.2 Calendar months

New:

1. Bioventus Rabbit Posterior Lateral Fusion Model BMP/Carrier Study (SOW #10)
Sponsor Agency: Bioventus LLC
8 St. Mary's Street, Boston, Massachusetts 02115
09/05/2017–12/05/2017, \$59,328.11 Total Direct Costs
Douglas C. Fredericks (PI), 0.12 Calendar months
Objective: Evaluate efficacy of BV-265/PCM in a rabbit model of posterolateral fusion for 2 doses of BV-265. Comparisons will be made with historical data for 8 week autograft (iliac crest bone graft) controls. Specimens from 16 week groups will be evaluated for residual ceramic compared to 8 week groups and unimplanted controls.
OVERLAP: There is no overlap.
2. Bioventus Rabbit Femur Core Defect dBMP (SOW #9)
Sponsor Agency: Bioventus LLC
8 St. Mary's Street, Boston, Massachusetts 02115
09/05/2017–12/05/2017, \$77,120.35 Total Direct Costs
Douglas C. Fredericks (PI), 0.12 Calendar months
Objective: Investigate resorption of trabecular bone resulting from implantation of BV-265 with PCM or NiTi carrier materials at a femoral condyle core defect site. Controls include BMP-2 on ACS, BV-265 on ACS, and PCM or NiTi with no BMP added.
OVERLAP: There is no overlap.
3. Assessment of AltaPore Lapine Posterolateral Fusion Model
Sponsor Agency: Baxter Healthcare Corporation
25212 W Illinois Route 120, Round Lake, Illinois 60073
Tel. 224-270-4335
06/08/2017–06/08/2022, \$624,914 Total Direct Costs
Douglas C. Fredericks (PI), 1.2 Calendar months
This is a master laboratory services corporation agreement with Baxter Healthcare Corp. for a rabbit study of their test article. The objective of this study is to evaluate the performance of AltaPore, a novel bone graft substitute composed of silicate substituted hydroxyapatite (SiHA) in an FDA-approved rabbit posterolateral spine fusion model. The goals of the study are to determine the effect of the test article (AltaPore) relative to autograft (ICBG) and Mastergraft Putty on the following outcomes: fusion rate (measured by palpation, motion analysis, radiography, CT, and histopathology), quantity and quality of new bone formed (measured by radiography, CT and histomorphometry), quantity and quality of graft resorption (measured by radiography, CT and histomorphometry), and host response (measured by histopathology).
OVERLAP: There is no overlap.
4. Evaluation of a New Ceramic-collagen Implant in a Sheep Intramuscular Osteoinduction Model
Sponsor Agency: Medtronic Sofamor Danek, Inc.
2600 Sofamor Danek Drive, Memphis, Tennessee 38132
07/28/2017–07/28/2018, \$73,020.75 Total Direct Costs
Douglas C. Fredericks (PI), 0.12 Calendar months

The use of allograft tissue is now commonplace; however, allograft tissue is prone to therapeutic risks related to tissue sourcing and immunological sensitivity. As a result of limitations in the standard of care, there is significant interest in the use of synthetic bone graft substitutes that can provide the structural matrix of allograft or autograft, followed by progressive and orderly remodeling of the implant into normal bone. Synthetic grafts that inherently mimic the inorganic chemistry of natural bone provide an attractive alternative to naturally sourced tissues due to the ability to generate multiple product variants of consistent high quality with no disease transmission risks. These manufactured grafts have the potential to have osteoconductive and osteoinductive properties in addition to low immunogenicity, low risk of disease transmission, and high accessibility. The objective of this study is to evaluate the osteoinductive properties of 3 different bone void fillers in comparison to a newly developed collagen-ceramic bone void filler in an ectopic site using quantitative histomorphometry analysis.

OVERLAP: There is no overlap.

5. Biomechanical Analysis of the Proximal Adjacent Segment Following Thoracolumbar Spine Multilevel Instrumentation

Sponsor Agency: Implanet America, Inc.

8 Faneuil Hall Marketplace, 3rd Floor, Boston, Massachusetts 02109

01/01/2017–12/31/2017, \$51,207 Total Direct Costs

Nicole M. Grosland, PhD (PI)

Douglas C. Fredericks (Co-Investigator), 0.12 Calendar months

Proximal junction kyphosis (PJK) is a common complication following multilevel instrumented fusion for spinal deformities. The objective of this project is to test if there is a biomechanical advantage to use the test article. The current study is to analyze the biomechanical properties of such hybrid constructs (pedicle screw/sublaminar band) using a cadaveric model. We specifically will determine whether such novel constructs impart a biomechanical advantage against the development of known risk factors for PJK.

OVERLAP: There is no overlap.

6. Sirakoss MaxSi TM Graft Putty Formulation Assessment in a Lapine Posterolateral Fusion Model

Sponsor Agency: SIRAKOSS

02/01/2016–12/01/2017, \$154,675.02 Total Direct Costs

Douglas C. Fredericks (PI), 0.24 Calendar months

This is a followup study to determine effects of different formulations of MaxSiTM Graft Putty to optimize the implant characteristics to facilitate stability of graft at the intended fusion site.

OVERLAP: There is no overlap.

Martin – Dr. Martin completed two ongoing grants, remains involved in an extended project and was on one new projected since the previous reporting period.

Completed:

1. Direct Delivery of Bone Morphogenetic Protein-2 and Fibroblast Growth Factor-2 Plasmid Genes for Diabetic Fracture Healing in a Rabbit Model
Sponsor Agency: American Orthopaedic Foot & Ankle Society
05/12/2015 – 10/31/2016, \$20,000 Total Costs
Nathan A. Nicholson, MD (PI)
James A. Martin, PhD (Co-Investigator), 0.12 Calendar months (no salary support)
2. Mitochondrial Based Treatments that Prevent Posttraumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model
W81XWH-11-1-0583
Sponsor Agency: United States Department of Defense, Army Medical Research Acquisition Activity
09/01/11 – 08/31/2017, \$2,559,912 Total Costs
James A. Martin, PhD (PI), 1.73 Calendar months (no salary support)

Extended:

1. CORT Innovations to Assess and Forestall Post-Traumatic Osteoarthritis
5 P50 AR055533-05
Sponsor Agency: US DHHS, National Institutes of Health/NIAMS
09/01/2012–08/31/2018, No Cost Extension, Award \$7,038,002
Joseph A. Buckwalter IV, MD, MS (PI)
James A. Martin, PhD (Co-Investigator), James A. Martin, PhD (Co-Associate Director, 0.12 Calendar months; Co-PI, Project 1, 0.96 Calendar months; PI, Joint Trauma Biomarker Core, 1.77 Calendar months)

New:

1. Do Changes in Thiol Metabolism Mediate Osteoarthritis Progression?
1 K99 AR070914-01A1
Sponsor Agency: US DHHS, National Institutes of Health/NIAMS
One Democracy Plaza, 6701 Democracy Blvd, Suite 800
Bethesda, Maryland 20892-4872
09/01/2017–08/31/2021, \$90,961 total costs K99
Mitchell C. Coleman, PhD (PI)
James A. Martin, PhD (Mentor), 0.6 Calendar months
Project description listed under Coleman
OVERLAP: There is no overlap with this work.

Willey – Dr. Willey had one grant end, one grant extended and four new grants begin since the previous reporting period.

Completed:

1. Engineering Endogenous Cartilage Repair
Sponsor Agency: Arthritis Foundation
01/01/2016–01/01/2019, \$892,057 Total Direct Costs
James A. Martin, PhD (PI)
Michael C. Willey, MD (PI), 0.6 Calendar months

Extended:

1. The Effect of Sirtuin-1 on Chondrocyte Progenitor Cell Activity in Acute Cartilage Injury
Sponsor Agency: Orthopaedic Trauma Association
01/01/2016–07/01/2018, \$20,000 total direct costs
Jocelyn Compton, MD (PI)
Michael C. Willey, MD (Co-PI, Mentor), 0.12 Calendar months (no salary support)

New:

1. Perioperative Screening and Nutritional Supplementation in Orthopaedic Trauma Patients
Sponsor Agency: Orthopaedic Trauma Association
9400 West Higgins Road, Suite 305
Rosemont, IL 60018
08/01/2017–07/31/2019, \$75,984 Total Direct Costs
Michael C. Willey, MD (Co-PI), 0.6 Calendar months
This project aims to demonstrate implementable screening tool and nutritional intervention that will lead to improved quality and patient safety and provide evidence-based Clinical Practice Guidelines that can be implemented in trauma centers. In order to achieve these aims we will 1) demonstrate the value of a simple objective screening tool to identify trauma patients at increased risk of postoperative complications due to poor functional status; 2) institute an achievable nutritional intervention that will decrease postoperative complications in trauma patients; 3) develop evidence-based Clinical Practice Guidelines that can be instituted in hospitals and on trauma services throughout the country to improve clinical quality of screening and postoperative patient safety.
OVERLAP: There is no overlap with this work.
2. Joint Contact Stress as a Tool for Clinical Decision Making in Periacetabular Osteotomy
Sponsor Agency: Orthopaedic Research and Education Foundation
9400 West Higgins Road, Suite 215
Rosemont, IL 60018-4975
07/01/2017–06/30/2020, \$209,804 Total Direct Costs
Michael C. Willey, MD (Co-PI), 1.2 Calendar months
Project description listed under Goetz
OVERLAP: There is no overlap with this work.
3. Does Contact Stress Better Predict PTOA and Patient Outcomes in Patients with Displaced Acetabular Fractures Following ORIF?
Sponsor Agency: Orthopaedic Trauma Association
9400 West Higgins Road, Suite 305
Rosemont, IL 60018
06/01/2017–05/31/2018, \$20,000 Total Direct Costs
Michael C. Willey, MD (Co-PI and Mentor), 1.2 Calendar months
This project aims to demonstrate implementable screening tool and nutritional intervention that will lead to improved quality and patient safety and provide evidence-based Clinical Practice Guidelines that can be implemented in trauma centers. In order to achieve these aims we will 1) demonstrate the value of a simple objective screening tool to identify trauma patients at increased risk of

postoperative complications due to poor functional status; 2) institute an achievable nutritional intervention that will decrease postoperative complications in trauma patients; 3) develop evidence-based Clinical Practice Guidelines that can be instituted in hospitals and on trauma services throughout the country to improve clinical quality of screening and postoperative patient safety.

OVERLAP: There is no overlap with this work.

4. Hip Fracture Plate Research Agreement

Sponsor Agency: Biomet Biologics, LLC

Clinical Affairs, 1800 West Center Street, Warsaw, Indiana 46580 (mailstop 4020)

11/10/2015–10/23/2018, \$96,875 Total Direct Costs

Michael C. Willey, MD (PI), 0.12 Calendar months

This is a clinical research study investigating the efficacy of a new hip fracture plate. It is a prospective, multi-center study that aims to document revision rate in comparison to literature values for cannulated screws and hip screws, and adverse event rates for comparison to the literature and/or retrospective cases.

OVERLAP: There is no overlap with this work.

7.3 Other Organization Involvement

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Updated Quad Chart attached

9. APPENDICES

None

Joint Distraction Treatments of Intra-articular Fracture-Induced Post-traumatic Osteoarthritis in a Large Animal Model

OR140355

W81XWH-15-1-0642

PI: Jessica E. Goetz, PhD

Org: University of Iowa

Award Amount: \$1,591,922



Study/Product Aim(s)

- Establish effect of delayed fracture fixation on PTOA development
- Determine efficacy of joint distraction for preventing PTOA when applied acutely after intra-articular fracture (IAF)
- Determine efficacy of mid-term joint distraction for reversing PTOA pathology that develops in the weeks after IAF
- Determine if articulated joint distraction results in superior tissue organization and tissue/joint function compared to static distraction

Approach

Building on previous work supported by W81XWH-10-1-0864 to create a large animal model of IAF-induced PTOA, this project will evaluate the ability of joint distraction to prevent or treat PTOA. In the first aim, joint distraction will be applied at the time of definitive fixation, and in the second aim, the joint will be distracted 12 weeks after fixation when the model is in early stages of PTOA pathology. Joint function, histological tissue structure, and cartilage biological function will provide outcome measures.



Accomplishments: We have developed an articulated joint distraction device. We have used this device in the final four live animal surgeries needed to complete Aim 1 experiments. This device will be used for Aim 2 studies beginning in Project Year 3.

Timeline and Cost

Activities	CY	2015	2016	2017	2018
Technique Developments (Distraction, Histology Analysis, μ CT Analysis, etc.)					
Aim 1 - Live Animal Work (Acute Distraction)					
Aim 2 - Live Animal Work (Mid-term Distraction)					
Data Analysis					
Estimated Budget (\$K)		\$60	\$501	\$636	\$394

Updated: 10/31/2017

Goals/Milestones

Goal 1 – Finalize distraction protocol

- ☒ Mechanical validation testing of distractor configuration

Goal 2 – Determine efficacy of immediate postoperative distraction

- Develop data analysis routines (histology, μ CT, confocal)
- Complete live animal work
- Analyze Specific Aim 1 data (mechanical/biological/histological)

Goal 3 – Determine efficacy of delayed joint distraction

- ☒ Finalize articulated distractor methodology
- ☐ Complete live animal work
- ☐ Analyze Specific Aim 2 data (mechanical/biological/histological)

Comments/Challenges/Issues/Concerns

- We need to apply for a no cost extension to accommodate an animal availability schedule causing survivals to extend beyond the current project end date.

Budget Expenditure to Date

Projected Expenditure: \$1,046,787 Actual Expenditure: \$832,154